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FIG. 1

The Enterohepatic Circulation with Key Transporter Proteins Mediating Bile Acid Circulation

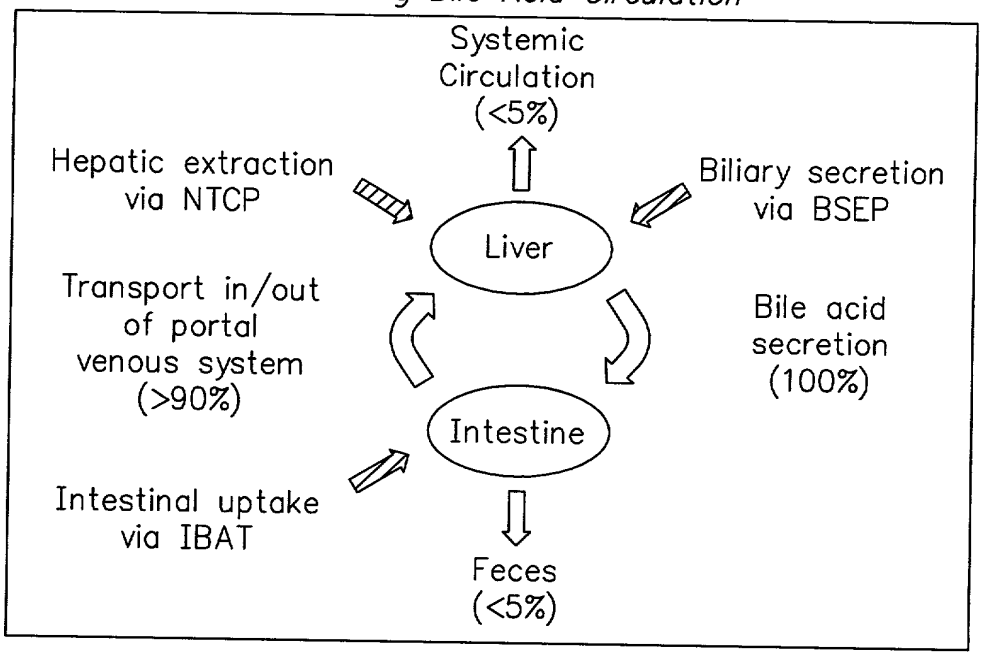


FIG. 8

Enterohepati Circulation Mediated by Intestinal Peptide and Hepatic Anion Transporters

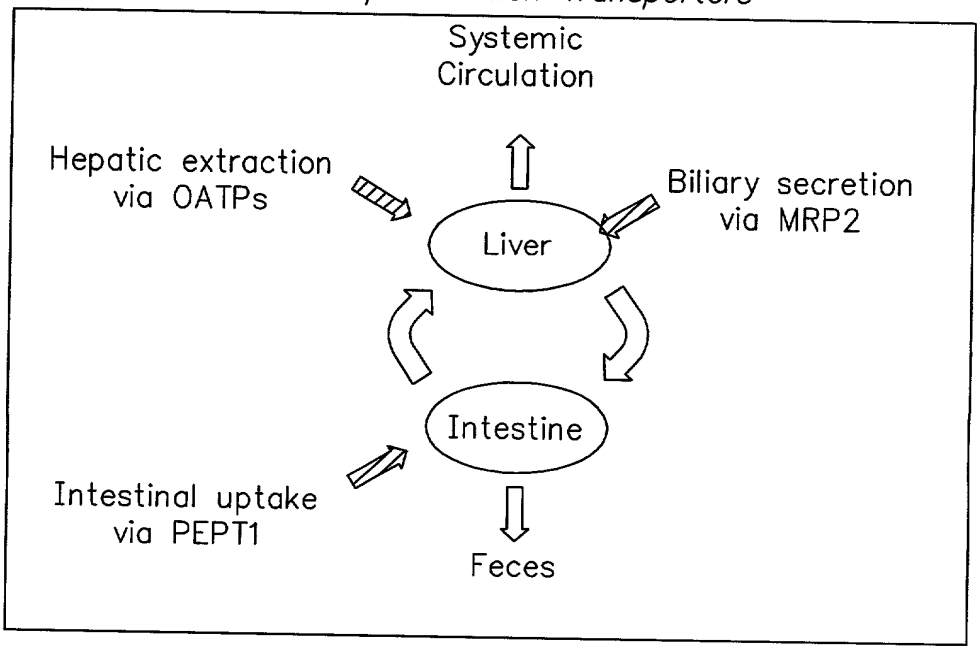
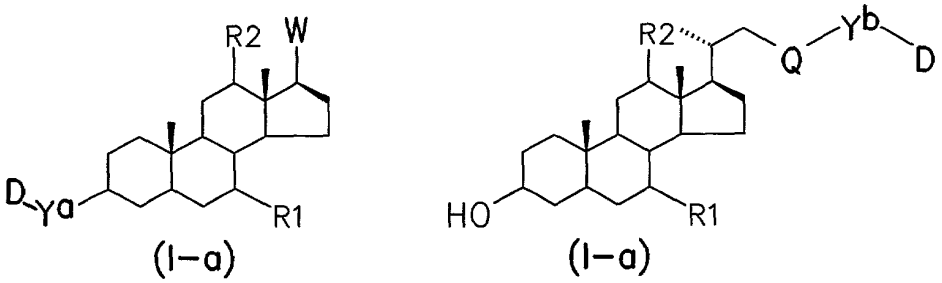


FIG. 2

Bile Acid Prodrug Derivatives for Sustained Release of Drugs

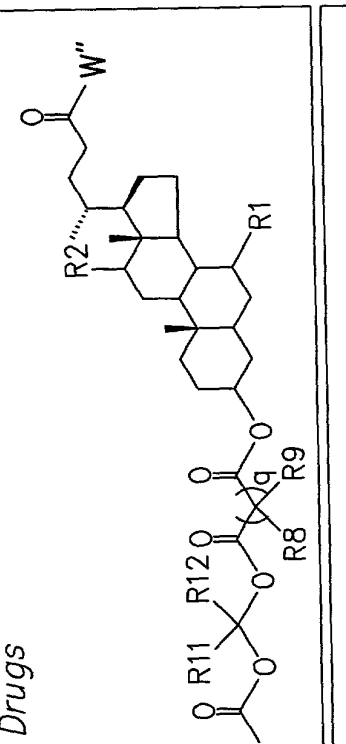


Y^a, Y^b are cleavable linker groups
D is a drug moiety
Q is CH_2 or O
W is selected from the group consisting of $-CH(CH_3)W'$ where W' is a substituted alkyl group containing a moiety which is negatively charged at physiological pH, which moiety is selected from the group consisting of $-COOH$, $-SO_3H$, $-SO_2H$, $-P(O)(OR^6)(OH)$, $-OP(O)(OR^6)(OH)$, $-OSO_3H$ and pharmaceutically acceptable salts thereof

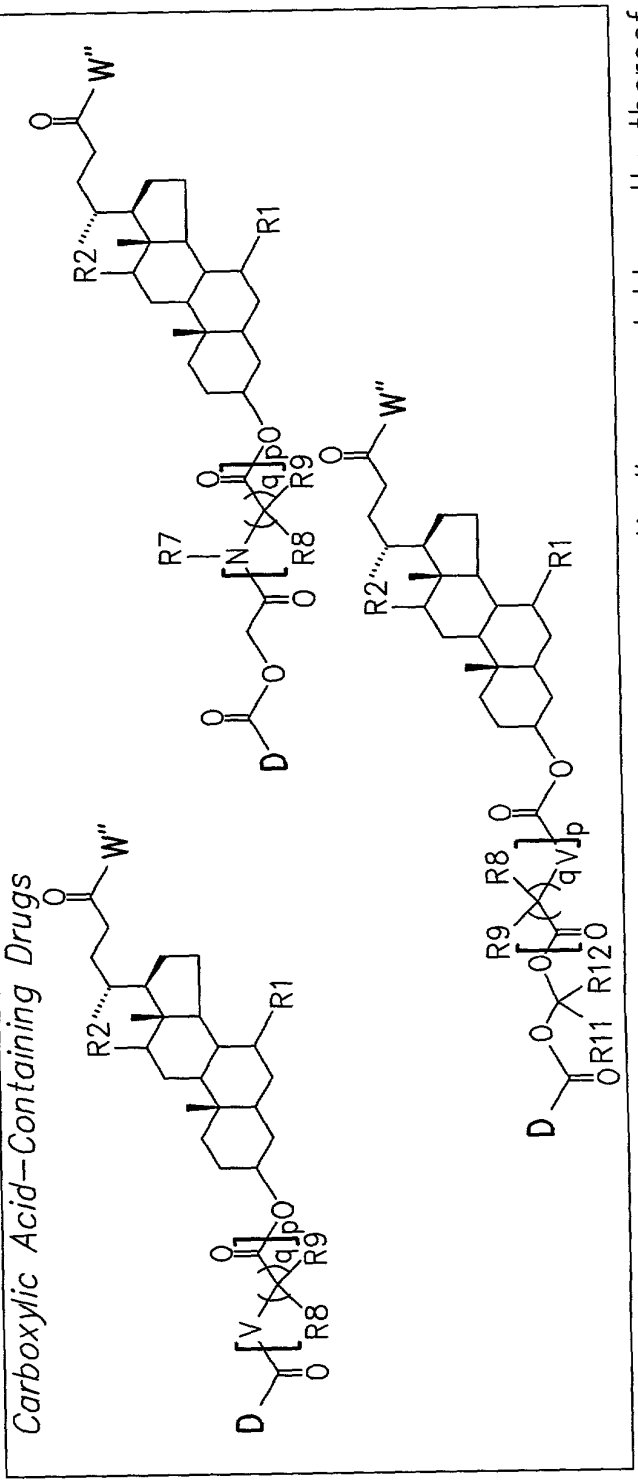
R1 = R2 = α−OH (from Cholate)
R1 = α−OH, R2 = H (from Chenodeoxycholate)
R1 = β−OH, R2 = H (from Ursodeoxycholate)
R1 = H, R2 = α−OH (from Deoxycholate)
R1 = β−OH, R2 = α−OH (from Ursocholate)
R1 = R2 = H (from Lithocholate)

FIG. 3 *Generic Structures of Preferred Bile Acid C-3 Derivatives*

Hydroxyl or 1° and 2° Amine-Containing Drugs



Carboxylic Acid-Containing Drugs



W" is OH , $NHCH_2CO_2H$, $NHCH_2CH_2SO_3H$ or pharmaceutically acceptable salts thereof

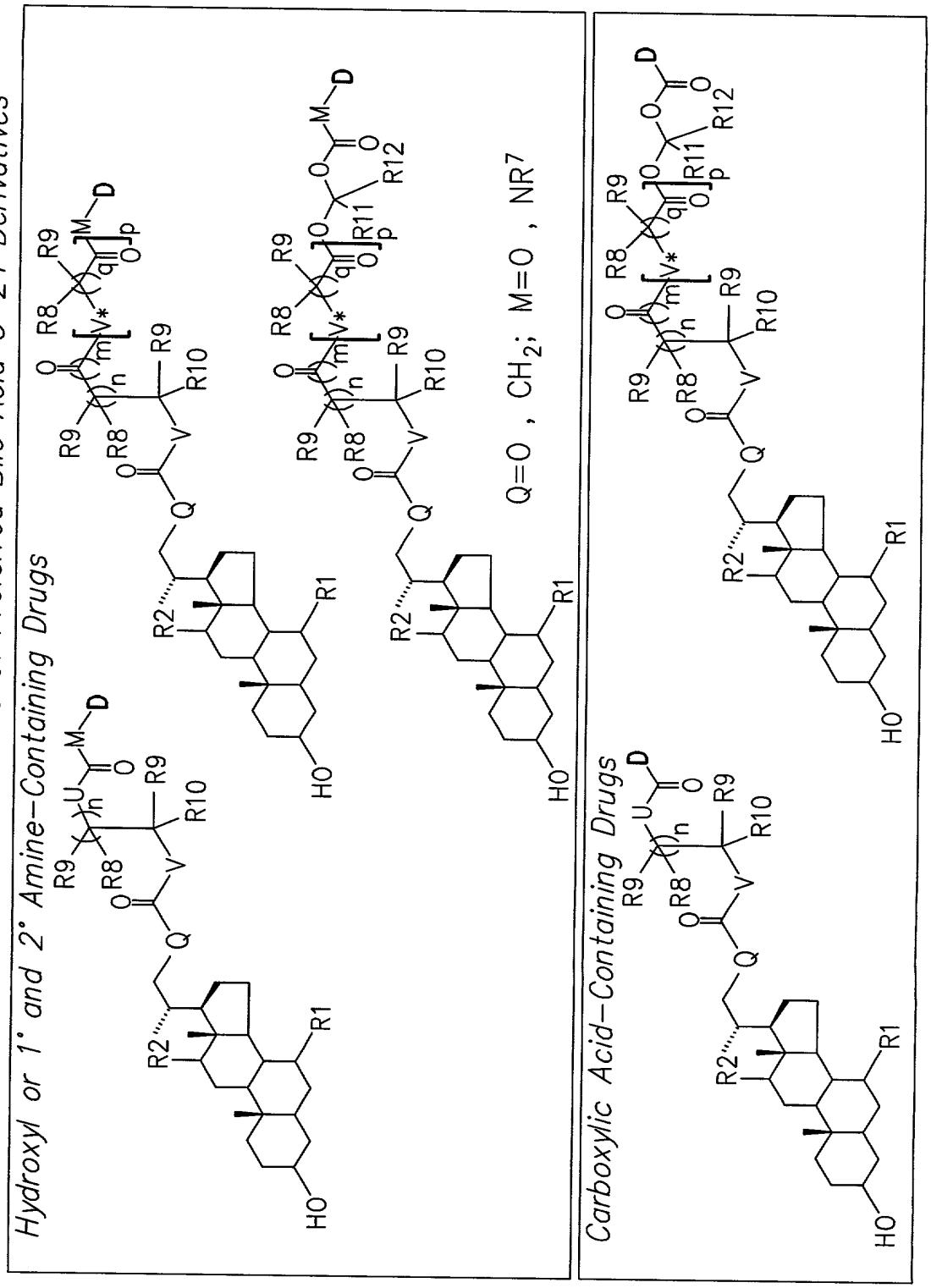


FIG. 4 *Generic Structures of Preferred Bile Acid C–24 Derivatives*

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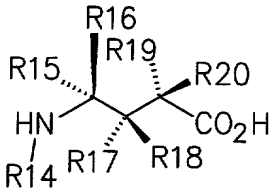
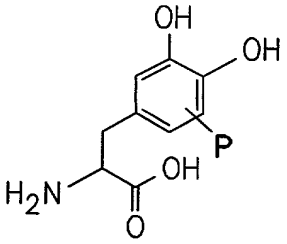
FIG. 5

GABA Analog Derivatives and L-Dopa Derivatives





Generalized GABA Analog *Optionally Protected L-Dopa Analog*

R14, R15, R16, R19 and R20 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl and substituted heteroarylalkyl;

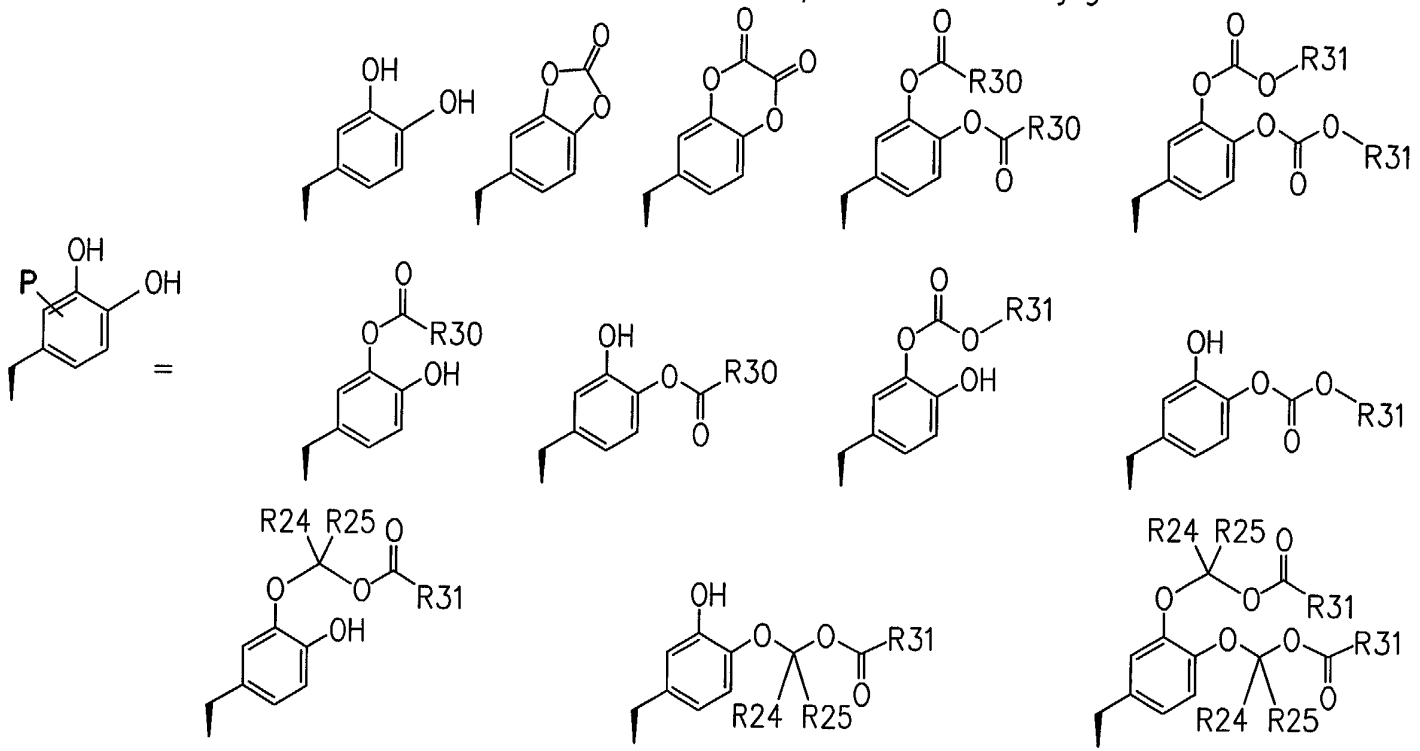
R17 and R18 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl and substituted heteroarylalkyl or optionally, R17 and R18 together with the carbon atom to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl or bridged cycloalkyl ring;

P is a catechol protecting group (see Figure 6)

The GABA analog or L-Dopa analog is attached to the steroid nucleus in (I-a) or (I-b) either by replacement of one of the amino hydrogen atoms, or a hydrogen atom from one of the hydroxy groups of the catechol, or the hydroxyl group of the carboxyl moiety by a covalent bond to Y^a or Y^b

FIG. 6

Catechol Protection Strategies Applicable for L-Dopa Bile Acid Conjugates



R30 = hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl

R31 = alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl

R24, R25 = hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or R24 and R25 together with the carbon to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycloalkyl or substituted heterocycloalkyl ring

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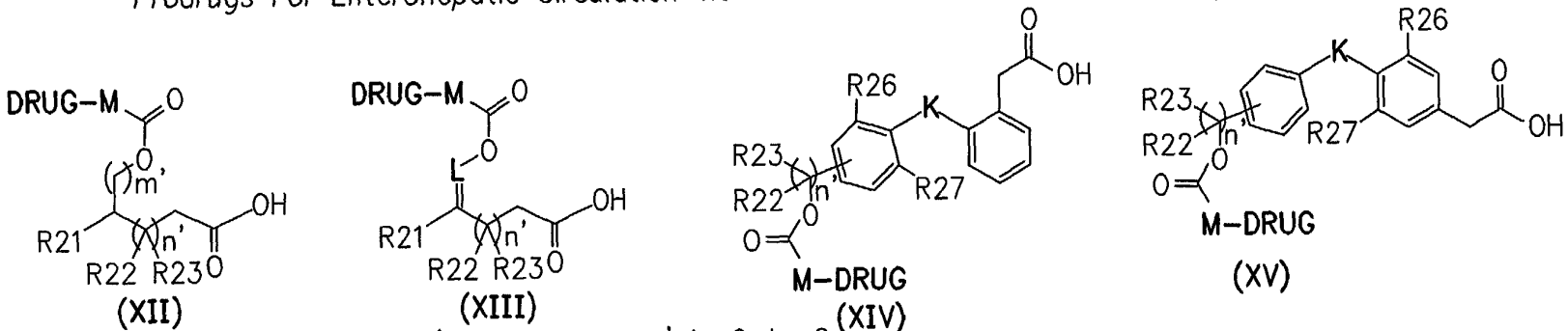
INVENTOR: MARK A. GALLOP ET AL.
APPLICATION SERIAL NO: 09/972,402 7 OF 16

FIG. 7

Prodrugs For Enterohepatic Circulation via Intestinal and Liver Anion Transporters



M = O , NR7 , CR8R9 m' is 0 to 6 ; n' is 0 to 6

L = CR8 , N

K = O , NR7 , CR8R9 ; $S(O)_j$, j=0, 1, or 2

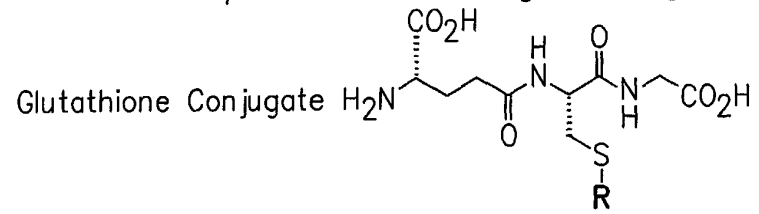
Each of R21 to R23 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, substituted acyl, acylamino, substituted acylamino, alklysulfinyl, substituted alkylsulfinyl, alkylsulfonyl, substituted alkylsulfonyl, alkylthio, substituted alkylthio, alkoxycarbonyl, substituted alkylthio, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxy, substituted aryloxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyloxy, substituted heteroalkyloxy, heteroaryloxy and substituted heteroaryloxy

Preferably R22 and R23 are independently selected from the group consisting of hydrogen, alkyl and substituted alkyl

R26 and R27 are independently selected from the group consisting of halo and lower alkyl (including branched alkyl)

FIG. 9

Enterohepatic Recirculating Prodrugs Based On Glutathione Mimetics

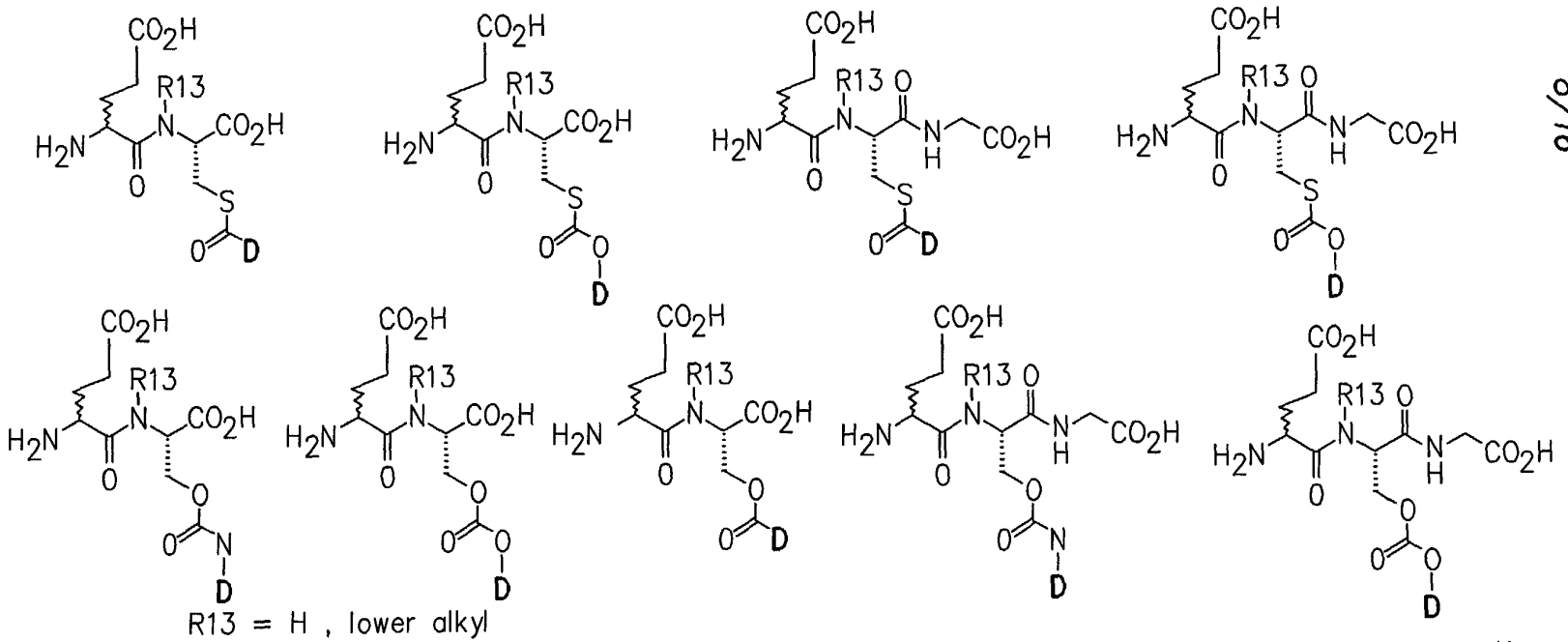


Substrate for OATP on sinusoidal membrane of liver

Substrate for MPR2 on canilicular membrane of liver

Not transported by PEPT1

Examples of Di– and Tripeptide Prodrugs of Hydroxyl, Amine and Carboxylic Acid–Containing Drugs Based on Glutathione–Like Motif



R13 = H , lower alkyl

Use PEPT1 substrate with metabolically stable di– or tripeptide backbone to achieve intestinal absorption

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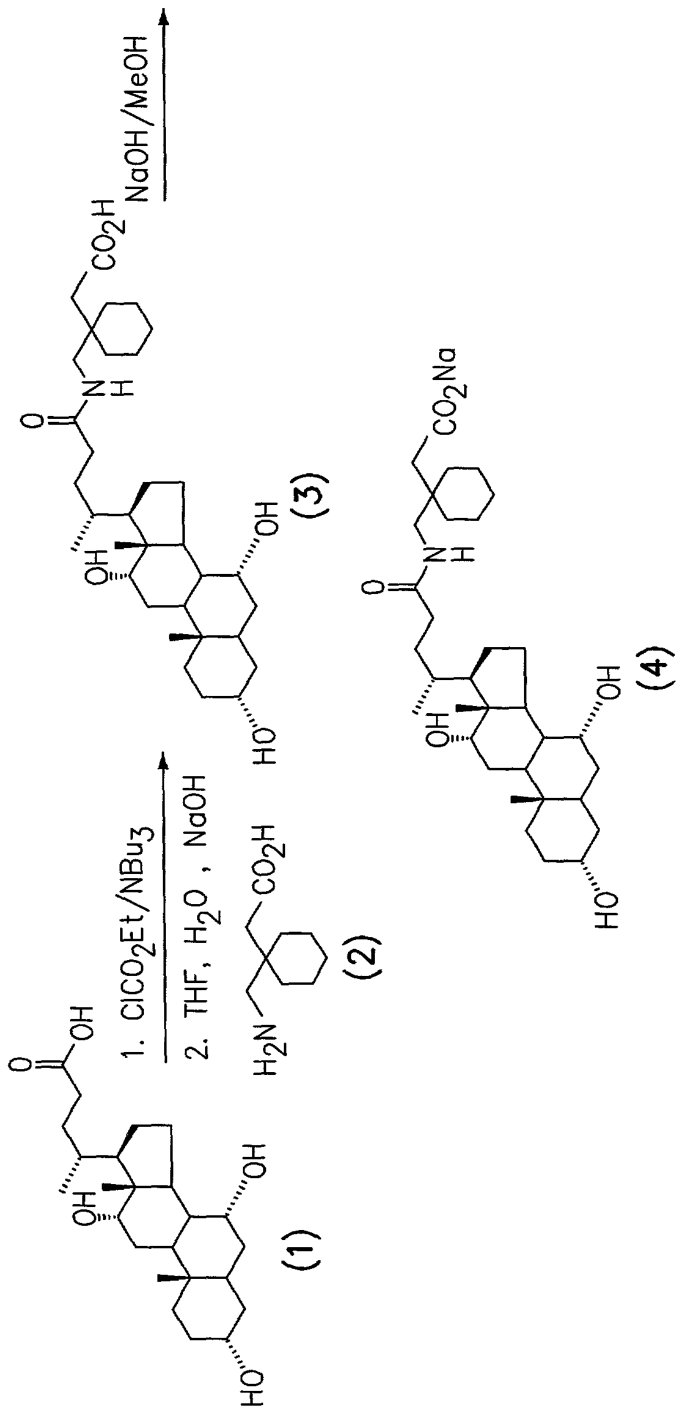


FIG. 10

FIG. 11

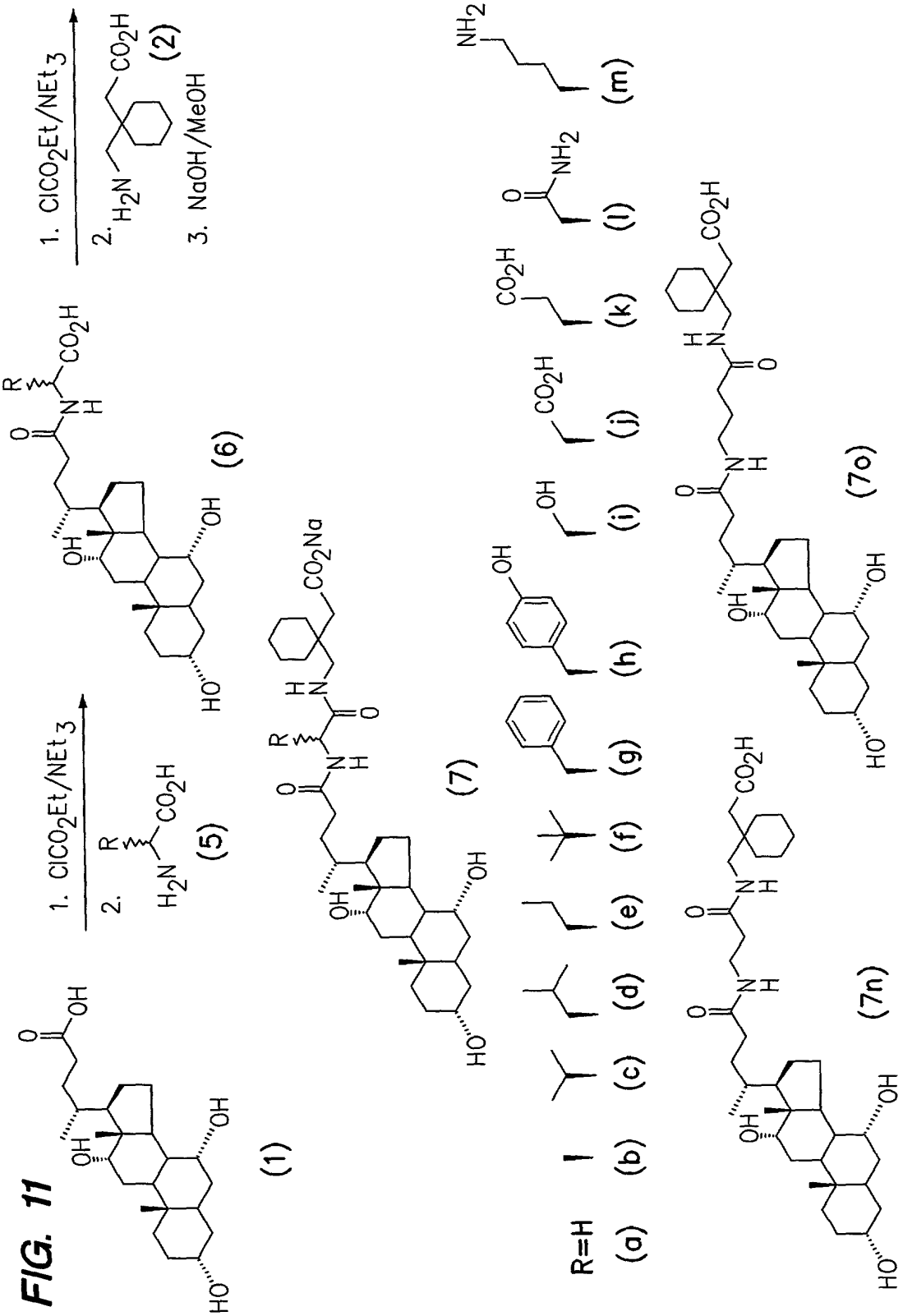

1. ClCO2Et/NEt3
2. H2N CO2H R
3. NaOH/MeOH
(1)
(2)
(5)
(6)
(7)
(7n)
(7o)
R=H
(a)
(b)
(c)
(d)
(e)
(f)
(g)
(h)
(i)
(j)
(k)
(l)
(m)

FIG. 12

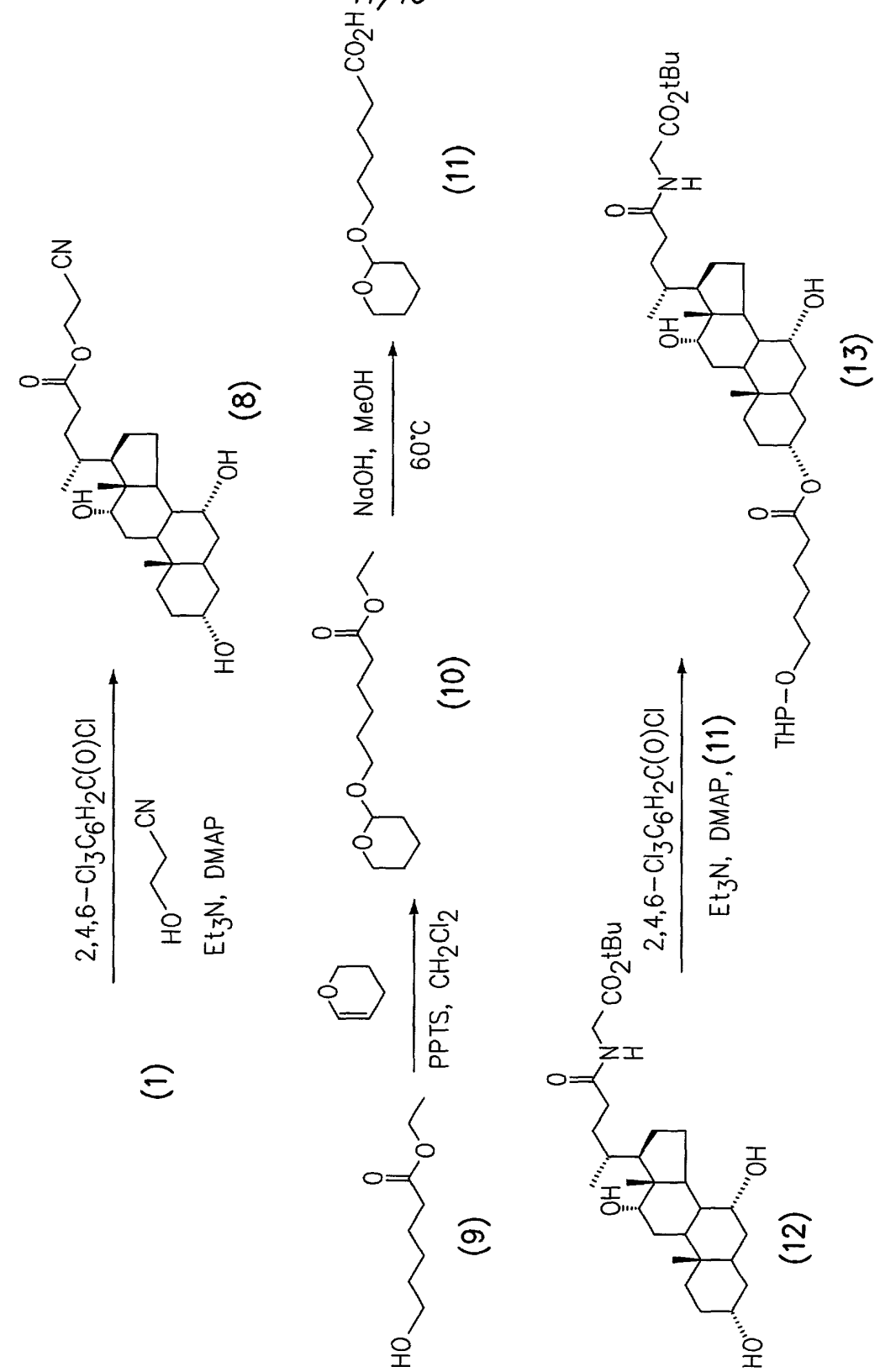
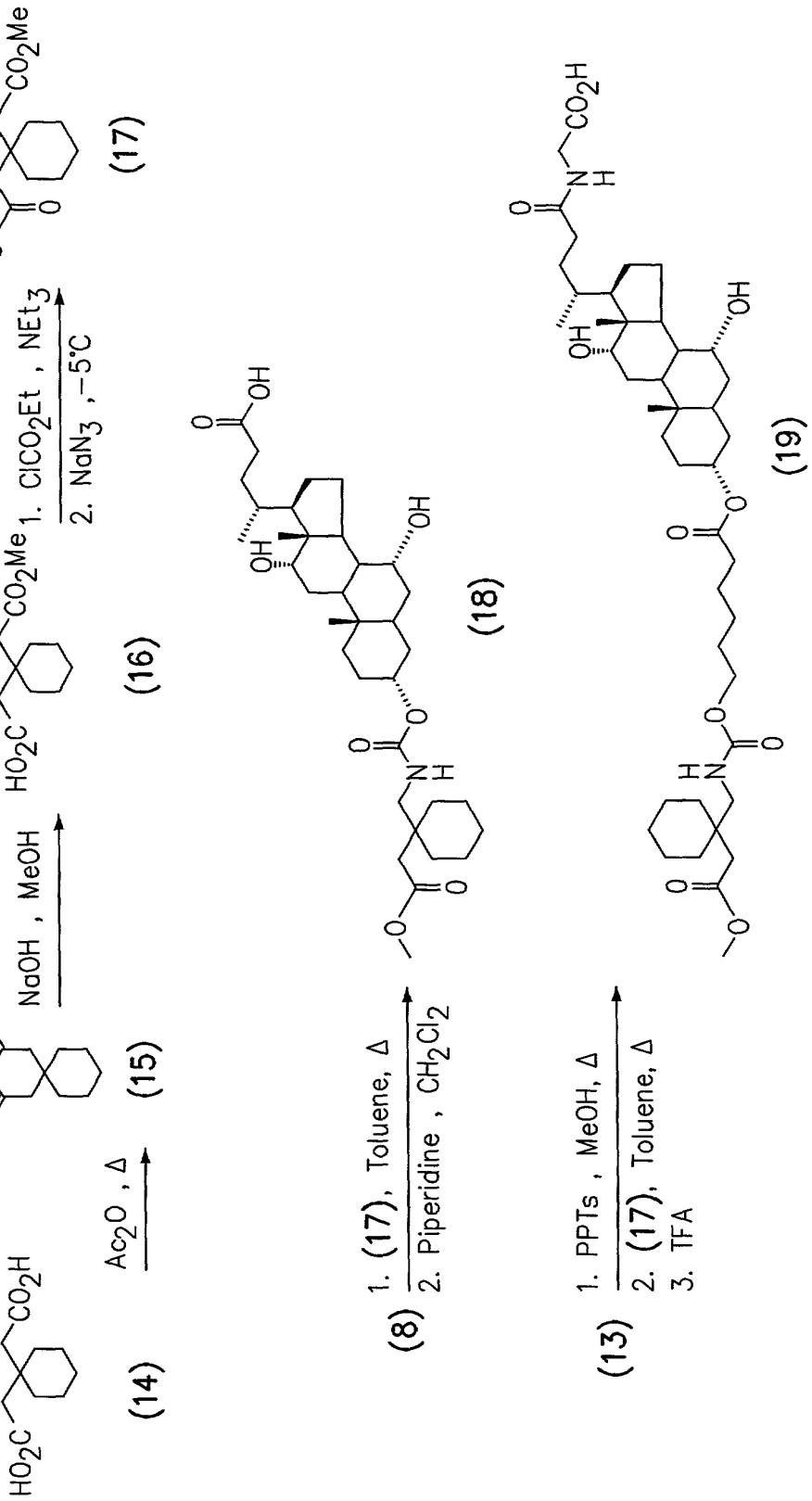

2,4,6-Cl3C6H2C(O)Cl
Et3N, DMAP
(1)
(8)
PPTS, CH2Cl2
(9)
(10)
NaOH, MeOH
60°C
(11)
2,4,6-Cl3C6H2C(O)Cl
Et3N, DMAP, (11)
(12)
(13)
THP-O
CO2tBu
CO2H
CN
OH
HO

FIG. 13


CO2Me
N3
O
(17)
1. ClCO2Et , NEt3
2. NaN3 , −5°C
CO2Me
HO2C
(16)
NaOH , MeOH
O
O
O
O
(15)
Ac2O , Δ
CO2H
HO2C
(14)
OH
O
OH
O
O
N
H
O
O
(18)
1. (17), Toluene, Δ
2. Piperidine , CH2Cl2
(8)
CO2H
N
H
O
OH
OH
O
O
O
O
O
N
H
O
O
(19)
1. PPTs , MeOH, Δ
2. (17), Toluene, Δ
3. TFA
(13)

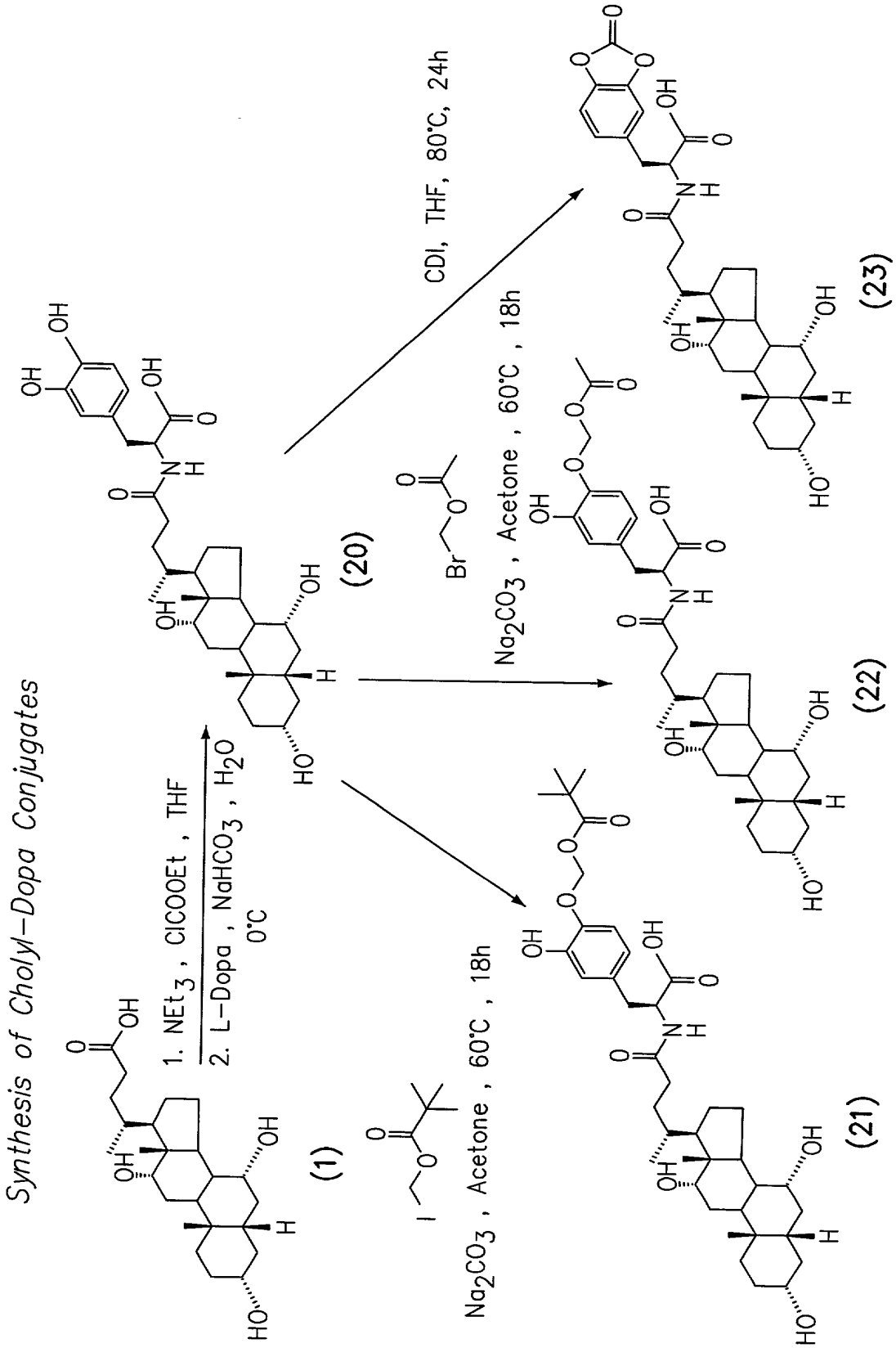


FIG. 14
Synthesis of Cholyl-Dopa Conjugates

FIG. 15

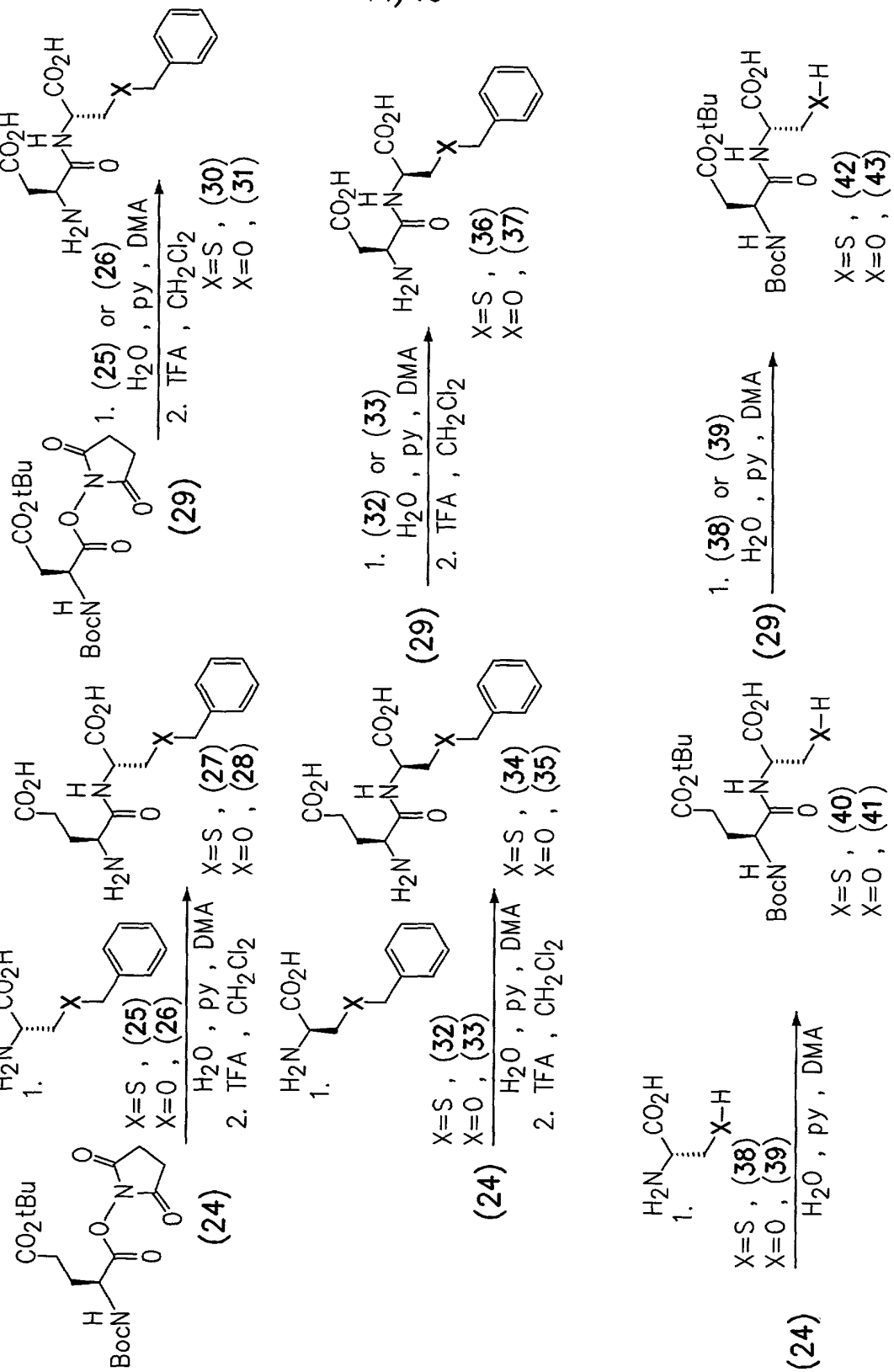

(24)
X=S , (25)
X=O , (26)
1. H2O , py , DMA
2. TFA , CH2Cl2
X=S , (27)
X=O , (28)
(29)
1. (25) or (26)
H2O , py , DMA
2. TFA , CH2Cl2
X=S , (30)
X=O , (31)
X=S , (32)
X=O , (33)
X=S , (34)
X=O , (35)
1. (32) or (33)
X=S , (36)
X=O , (37)
X=S , (38)
X=O , (39)
1. (38) or (39)
X=S , (40)
X=O , (41)
X=S , (42)
X=O , (43)

FIG. 16

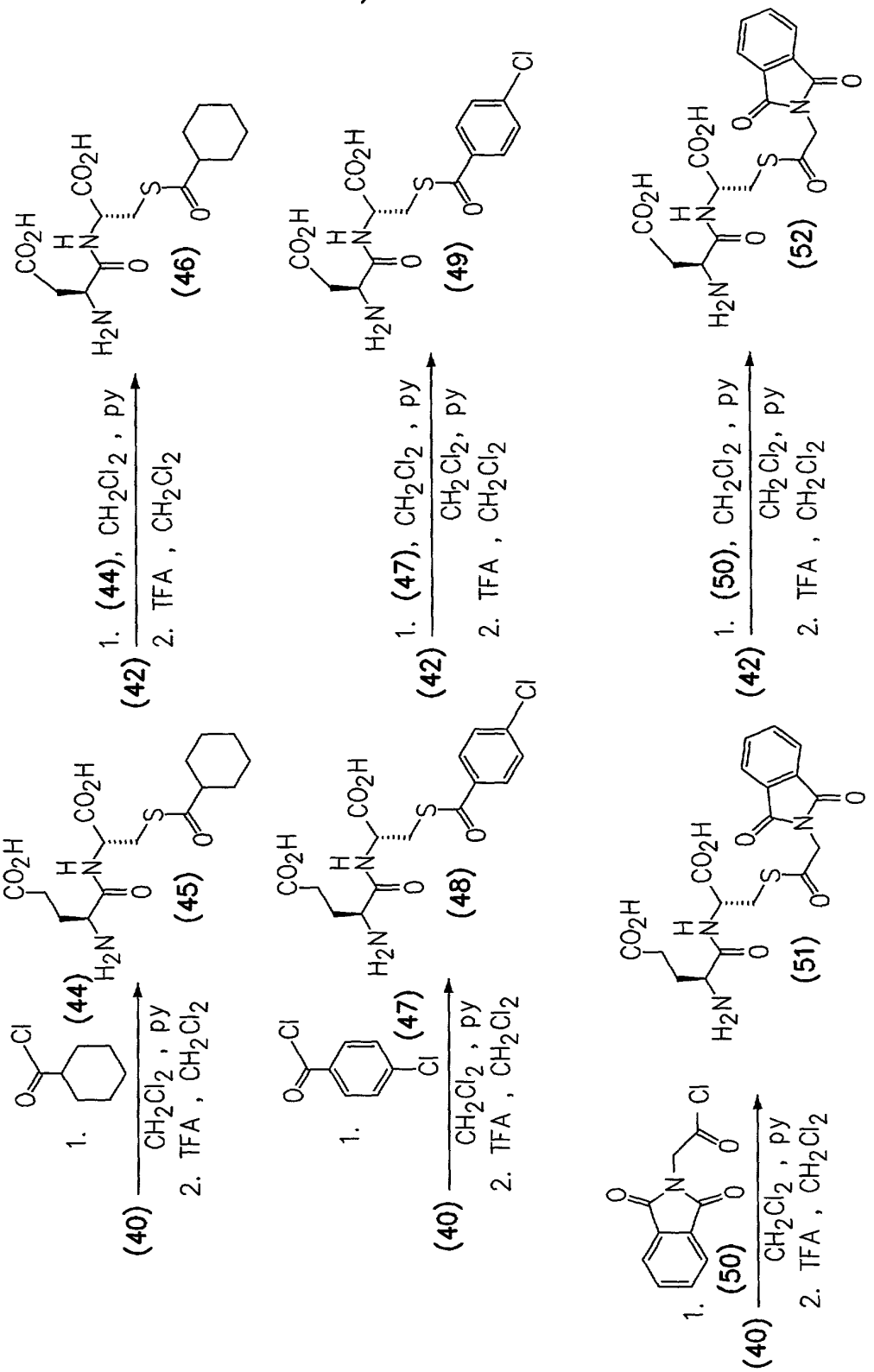
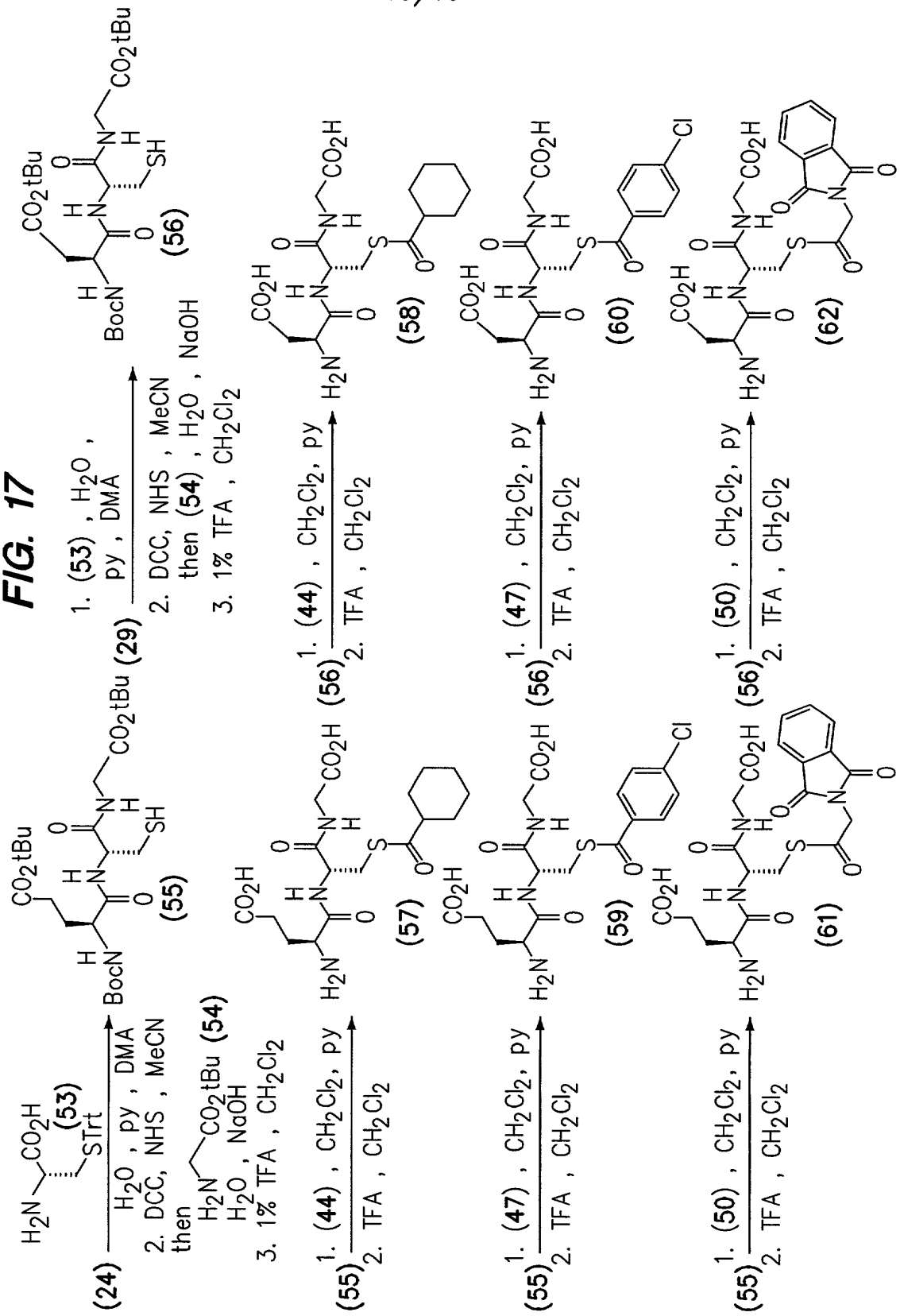

(40)
1.
2. TFA , CH_2Cl_2
CH_2Cl_2 , py
(44)
(45)
(47)
(48)
(50)
(51)
(42)
1. (44), CH_2Cl_2 , py
2. TFA , CH_2Cl_2
(46)
1. (47), CH_2Cl_2 , py
2. TFA , CH_2Cl_2
(49)
1. (50), CH_2Cl_2 , py
2. TFA , CH_2Cl_2
(52)

FIG. 17


(24)
(53)
1. (53), H2O, py, DMA
2. DCC, NHS, MeCN then (54), H2O, NaOH
3. 1% TFA, CH2Cl2
(29)
(54)
(55)
(56)
1. (44), CH2Cl2, py
2. TFA, CH2Cl2
(57)
(58)
1. (47), CH2Cl2, py
2. TFA, CH2Cl2
(59)
(60)
1. (50), CH2Cl2, py
2. TFA, CH2Cl2
(61)
(62)